DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
HFI-35 MD59111

60 8th Street, N.E.
Atlanta, Georgia 30309

March 18, 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Raymond E. Faulk
Vice President
Dihoma Chemical and Manufacturing, Inc.
195 Drew Road
Mullins, South Carolina 29294

WARNING LETTER
(99-ATL-11)

Dear Mr. Faulk:

An inspection of your facility was conducted on January 20-22, 1999, by Investigators Leah M. Andrews and Eric S. Weilage. Our inspection found that you manufacture and market "Protect U-2000," an aerosolized pediculicide for over-the-counter (OTC) human use under the CDF Enterprises div. of DiHoMa label.

The aerosolized product is labeled as containing the active ingredients pyrethrins extract and piperonyl butoxide for the treatment of body lice, head lice, crabs, nits, and chiggers on humans. The labeling states further that "Protect U-2000 is the only FDA approved Aerosol ... for direct application on HUMAN SKIN ... for Head Lice, Body Lice, Crab Lice and Chiggers ... ." The product is, therefore, a drug as defined in section 201(g) of the Federal Food, Drug and Cosmetic Act (the Act).

Pediculicide drug products for OTC human use are covered by the final rule at Title 21, Code of Federal Regulations (21 CFR), Parts 358.601 through 358.650. The final rule was published in the Federal Register of December 14, 1993. In that document the FDA specifically classified the active ingredients pyrethrum extract (formerly named pyrethrins) and piperonyl butoxide in an aerosol dosage form as nonmonographed, i.e., not generally recognized as safe and effective. These aerosol pediculicide preparations are specifically listed as nonmonographed under regulations 21 CFR 310.545(a)(25)(ii) which became effective on June 14, 1994. This specific section is part of a list of many OTC active ingredients and preparations under 21 CFR 310.545 that may not be marketed without an approved New Drug Application (NDA). The remaining part of the final rule covering non-aerosol pediculicides became effective on December 14, 1994.

In addition, the final rule for pediculicide drug products for OTC human use does not permit any claims for the treatment of chiggers. It does allow for the presence of a fine-tooth comb to be included to help in the removal of dead lice and nits, but it does not allow for the treatment of nits.

Based both on the formulation in an aerosol dosage form and on the claims for the treatment of chiggers and nits, "Protect U-2000" is a new drug as defined in section 201(p) of the Act in violation of section 505(a) of the Act and may not be marketed because it is not covered by an approved NDA.

"Protect U-2000" is also misbranded (502(a) of the Act) because its labeling is false and misleading. The product is not "The only FDA approved Aerosol" for use as an OTC pediculicide as stated in the labeling. It is not approved by the FDA, and the product as formulated and labeled is not generally recognized as safe and effective. Because the product is not approved by the FDA, it also fails to bear adequate directions for use and is further misbranded (502(f)(1) of the Act).

The inspection also revealed numerous significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in 21 CFR, Part 211. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Act.

You have failed to provide an appropriate facility for the manufacture, processing, packing, and holding of your drug products. The current structure was not of a suitable size or construction to facilitate cleaning, maintenance and proper operations. No separate clearly defined areas exist for manufacturing, packaging, labeling or storage of materials. The manufacturing facility is a barn-like structure and many of the walls and ceilings consist of exposed insulation and/or wood. The structure does not provide adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, and in-process materials and to prevent contamination. The facility is severely overcrowded. Raw materials, finished product and a variety of miscellaneous items, unrelated to drug manufacture, are stored throughout the facility. Raw materials and storage containers are not always clearly labeled as to their status and in some cases are not labeled at all.

You have failed to establish the adequacy of the cleaning methods currently in use. The available cleaning procedures were vague and seriously deficient. The procedures failed to describe what equipment was to be cleaned, the manner in which equipment was to be cleaned, and who was responsible for cleaning. These procedures have never been validated to establish their adequacy, suitability, or ability to remove potential contaminants. Pharmaceutical and nonpharmaceutical products (including a variety of industrial cleaners) are produced on the [redacted]fill line. Pharmaceutical products and industrial cleaners are manufactured in common tanks and filling lines with no documentation of cleaning prior to use. Cleaning records are nonexistent. The adequacy of your cleaning procedures is critical in that no equipment is solely dedicated for pharmaceutical use and equipment use logs are not maintained.

You have failed to establish appropriate approved master production and control records for the drug products you manufacture. You have failed to establish specific instructions for the manufacture and testing of these products to include mixing times, sample weights, and sampling instructions. Each significant step is not documented in the batch records. Significant manufacturing steps had no record of verification by a second responsible individual. No comparison is made of the actual yields obtained to the theoretical yields expected. No documentation exists to indicate that the product labeling was verified and appropriately reconciled. Batch records failed to consistently record the lot numbers of raw materials used.

You have failed to implement sufficient controls to assure that incoming raw materials meet appropriate written specifications of identity, strength, quality, and purity. No identity testing is performed on each drug component as required. No verification is conducted to determine the reliability of the suppliers' certificates of analysis for raw materials utilized.

You have failed to implement appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. No formalized approved finished product specifications were available for your drug products. You could provide no analytical data for any batch of finished drug product manufactured at your location. You had failed to conduct any evaluation of the need for microbiological testing for the topical ointment [redacted] you manufacture. No determination had been made as to whether the product could support the growth of microorganisms.

You could not provide any documented evidence which established a high degree of assurance that the current manufacturing procedures and processes were effective and could consistently produce a product meeting its predetermined specifications and quality attributes. None of your manufacturing processes had been validated to assure that each batch would meet its purported identity and strength. You could provide no assurance that your drug products meet applicable standards of identity, strength, quality, and purity throughout their labeled expiration date. You could provide no stability data justifying the three year expiration date currently placed on [redacted] or Protect U-2000 products.

You have failed to ensure that each person engaged in the manufacture, processing, packing, or holding of your drug products, and each person responsible for supervising these activities, has the education, training, and experience to enable that person to perform their assigned functions in such a manner as to provide assurance that your drug products have the quality and purity that they purport to or are represented to possess. This training must not only be in the particular operation that the employee performs but also include current good manufacturing practice as it relates to the employee's functions. It is readily apparent that no one at your firm has received training commensurate with their responsibilities as evidenced by the lack of familiarity with the most basic GMP requirements. A copy of the GMPs was provided to you by our investigators. This lack of understanding is also exemplified by your stated belief that receipt of an NDC labeler code was paramount to FDA approval for the manufacture of the pediculicide product.

Many of the above deviations were included on the FDA 483 (Inspectional Observations) which was issued to, and discussed with, you at the conclusion of the inspection. The violations noted in this letter and in the FDA 483 are symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of any additional steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. We are in receipt of your February 4, 1999, response letter which included an assortment of new procedures. The response really did not address many of the specific problems noted on the FDA 483 and it was difficult to relate the new procedures to the noted deviations.

Your response to this Warning Letter should address your proposed actions regarding products currently in distribution and stored at your facility. You have indicated verbally that Dihoma plans to discontinue distribution of the Protect U-2000. Your response should specifically address this issue. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely,

Ballard H. Graham, Director
Atlanta District